The [^{18}F]Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man

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SUMMARY **A method has been developed to measure local glucose consumption in the various structures of the brain in man with three-dimensional resolution. [^{18}F]-2-deoxy-2-fluoro-D-glucose is used as a tracer for the exchange of glucose between plasma and brain and its phosphorylation by hexokinase in the tissue. A mathematical model and derived operational equation are used which enable local cerebral glucose consumption to be calculated in terms of the following measurable variables. An intravenous bolus of [^{18}F]-2-deoxy-2-fluoro-D-glucose is given and the arterial specific activity monitored for a predetermined period of from 30 to 120 minutes. Starting at 30 minutes, the activity in a series of sections through the brain is determined with three-dimensional resolution by an emission tomographic scanner. The method was used to measure local cerebral glucose consumption in two normal volunteers. The values in gray matter structures range from 5.79 mg/100 g per minute in the cerebellar cortex to 10.27 in the visual cortex, whereas, in white matter structures, the values range from 3.64 mg/100 g per minute in the corpus callosum to 4.22 in the occipital lobe. Average values for gray matter, white matter, and whole brain metabolic rates, calculated as a weighted average based on the approximate volume of each structure, are 8.05, 3.80, and 5.90 mg/100 g per minute, respectively. The value of 5.9 mg/100 g per minute compares favorably with values previously reported.** *Circ Res 44: 127-137, 1979*

THE ABILITY to measure regional cerebral blood flow in man has greatly increased our understanding of cerebral hemodynamics, particularly in pathophysiological states. The ability to detect alterations in local cerebral metabolism in man would be valuable in advancing our understanding of many disorders of the brain. We have developed such a technique which uses [^{18}F]-2-deoxy-2-fluoro-D-glucose ([^{18}F]-FDG).

The development of the Kety-Schmidt technique for the quantitative measurement of cerebral blood flow in man made it possible to determine the average rates of glucose utilization in the brain as a whole from measurements of blood flow and the cerebral arteriovenous difference of glucose (Kety and Schmidt, 1948). This method has added significantly to our knowledge of cerebral metabolism in normal and pathological states even though it provides only an average value for the whole brain. A method to measure hemispheric cerebral glucose uptake has been developed which also makes use of blood flow and arteriovenous difference measurements (Meyer and Shinohara, 1970). Recently, the basis for the use of ^{11}C-glucose for the measurement of regional cerebral glucose utilization has been published (Raichle et al., 1978). However, no regional measurements have been reported as yet, and the method has not been applied to man. Because it is often not possible to detect regional changes in metabolism from measurements in mixed cerebral venous blood, and because many disorders as well as many physiological changes affecting the brain occur on a regional basis, it would be useful to make regional measurements of glucose utilization in the brain in man.

A method has been developed for the measurement of regional cerebral oxygen uptake (Ter-Pogossian et al., 1970), but this technique has not been used to obtain truly regional information with three-dimensional resolution. The technique we have developed for measuring the local cerebral metabolic rate for glucose ($LCMR_{gl}$) does give such three-dimensional information. Furthermore, glucose utilization is stoichiometrically related to oxygen consumption in the aerobic state, except in a few situations such as starvation and insulin hypoglycemia, and provides a measure of energy metabolism in the anaerobic state as well.

The present technique is based on the previously described (Sokoloff et al., 1977) [^{14}C]-2-deoxyglu-

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cose ([^{14}C]-DG) method for measuring $LCMR_{gl}$ autoradiographically in animals. In this method, [^{14}C]-DG is used as a tracer for the exchange of glucose between plasma and brain and is phosphorylated by hexokinase in the tissues. [^{14}C]-DG is used because the labeled product, [^{14}C]-deoxyglucose-6-phosphate, is essentially trapped in the tissue over the time course of the measurements. A model was designed based on the assumptions of a steady state for glucose consumption, a first-order equilibration of the free [^{14}C]-DG pool in the tissue with the plasma level, and relative rates of phosphorylation of [^{14}C]-DG and glucose determined by their relative concentrations in the precursor pools and their respective kinetic constants for the hexokinase reaction. The following operational equation based on this model has been derived in terms of determinable variables:

$$R = \frac{C_T^*(T) - k_1^* e^{-(k_2^*+k_3^*)T} \int_0^T C_p^* e^{(k_2^*+k_3^*)t} dt}{\left[\frac{\lambda \cdot V_{max}^* \cdot K_m}{\phi \cdot V_{max} \cdot K_m^*}\right]\left[\int_0^T (C_p^*/C_p)dt - e^{-(k_2^*+k_3^*)T} \int_0^T (C_p^*/C_p) e^{(k_2^*+k_3^*)t} dt\right]} \quad (1)$$

where R = the calculated rate of glucose consumption per gram of tissue; C_T^* = the concentration of DG + DG-6-PO_4 in the tissue; C_p^* and C_p = the arterial plasma concentrations of DG and glucose, respectively; k_1^*, k_2^*, and k_3^* are the rate constants for the transport from plasma to the tissue precursor pool, for the transport back from tissue to plasma, and for the phosphorylation of DG in the tissue, respectively; λ = the ratio of the distribution volume of DG in the tissue to that of glucose; ϕ = the fraction of glucose that, once phosphorylated, continues down the glycolytic pathway; and K_m^* and V_{max}^* and K_m and V_{max} are the kinetic constants of hexokinase for DG and glucose, respectively. The latter six constants can be combined into one constant, which has been designated the lumped constant ($\lambda \cdot V_{max}^* \cdot K_m / \phi \cdot V_{max} \cdot K_m^*$).

The extension of this method to man requires the use of a tracer (radiopharmaceutical) that satisfies the following criteria: (1) The tracer must be taken up by the brain at a rate proportional to that of glucose, and its metabolic products must remain within the tissue in a known form, as is the case with DG. (2) The tracer must be labeled with a γ-emitting radionuclide which is chemically stable in vivo and which can be detected through the skull using emission tomography. (3) The radiation exposure resulting from the use of this tracer must be safe.

A labeled analogue to DG which appears to satisfy these requirements is [^{18}F]-FDG. Previous studies had shown that FDG, like DG, is a good substrate for yeast hexokinase (Bessell et al., 1972). Furthermore, fluorine-18 decays by positron emission, upon annihilation produces two 511-keV photons, and has a short half-life (110 minutes), thereby meeting the requirements for external detection and acceptable radiation dosimetry.

Because [^{18}F]-FDG had not been synthesized previously; a novel synthetic route to FDG, which was used in the ^{18}F labeling, was devised (Ido et al., 1978). [^{18}F]-FDG as well as [^{14}C]-FDG was used in studies to determine whether the former would be a suitable tracer for use in man.

Methods

Radiopharmaceuticals

[^{18}F]-FDG

The direct fluorination of 3,4,6-tri-*O*-acetyl-D-glucal with high specific activity [^{18}F]-fluorine (Casella, V., Ido, T., and Wolf, A. P., unpublished observation) gave [^{18}F]-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranosyl fluoride, which was hydrolyzed to [^{18}F]-FDG (Ido et al., 1978). The radiochemical purity was >98% as determined by thin layer chromatography on cellulose using isobutyric acid-ammonia-water (66:1:33), R_f = 0.67. Pharmaceutical quality [^{18}F]-FDG in isotonic saline for use in the human studies was sterilized by terminal Millipore (0.22 μm) filtration. The preparation was carried out according to a protocol that was demonstrated on three successive runs to yield a sterile, pyrogen-free product.* The specific activity† of [^{18}F]-FDG at the end of synthesis (i.e., the time when preparation of injectible radiopharmaceutical is completed) was 11 mCi/mg and 16 mCi/mg for the two human studies.

[^{14}C]-FDG

D-{U[^{14}C]}-glucose (from Amersham/Searle or Schwarz/Mann) was converted to [^{14}C]-3,4,6-tri-*O*-acetyl-D-glucal, which was then converted to [^{14}C]-FDG by two methods. (1) Fluorination with trifluoromethyl hypofluorite (CF_3OF), according to the method of Adamson et al. (1970), gave [^{14}C]-FDG in >98% radiochemical purity as determined by thin layer chromatography on silica gel with ethanol-ethyl acetate (1:1), R_f = 0.67, with a specific activity of 1.35 mCi/mmol. (2) Fluorination with molecular fluorine as described above gave [^{14}C]-FDG in 98%

* Tests for sterility and apyrogenicity were performed by South Shore Laboratory, Islip, New York, and Leberco Laboratories, Roselle Park, New Jersey.

† The specific activity can be increased or decreased to suit the requirements of a particular study by changing the amount of ^{18}F-F_2 or substrate used in the synthesis.

radiochemical purity with a specific radioactivity of 2.94 mCi/mmol.

Determination of Three-Dimensional Distribution of Activity in Brain

The three-dimensional distribution of ^{18}F activity in the brain was quantified by radionuclide-computed tomography with a Mark IV scanner (Kuhl et al., 1977a). The instrument is a four-sided arrangement of 32 independent detectors which continuously rotate as a unit, processing and displaying the reconstructed data while the study progresses. Detection is by single photon counting. The accumulated data are processed by a Varian 620/i digital computer, which makes corrections to equalize the detector response and to compensate for photon attenuation in the head. An iterative reconstruction technique called Cumulative Additive Tangent Correction is used to form the matrix of the distribution of activity for each cross-section of the head. The count distribution of the reconstructed section is then converted to units of activity concentration by relating it to the count distribution of a reference cylinder reconstruction for which the activity concentration is known. Brain cross-sections at different levels are obtained by moving the subject's head further into or out of the scanner and then repeating the scan. The Mark IV scanner is a high-sensitivity instrument with approximately uniform resolution throughout the section plane. The spatial resolution in terms of full-width-at-half-maximum (FWHM) of the reconstructed image of a line source of ^{18}F is 1.7 cm in the center and 1.6 cm at the edges of the section plane. Perpendicular to the section plane (i.e., section thickness), the FWHM is approximately the same. Estimates of activity concentration based on count summations in 2- by 2-cm regions of a section scan have a coefficient of variation of approximately 5%. Accuracy and reproducibility of these estimates are independent of location in the scan field and independent of differences in neighboring activities (Kuhl et al., 1977).

Suitability of Biochemical Properties of FDG

The use of FDG to measure local cerebral glucose utilization is based on the assumption that its biochemical properties are similar to those of DG. The essential properties are: (1) it is transported and competes with glucose for phosphorylation by cerebral hexokinase to their respective hexose phosphates; and (2) fluorodeoxyglucose phosphate, once formed, is sufficiently slowly degraded that it can be considered essentially trapped during the period of measurement. This presumption was tested by two types of experiments.

To confirm that FDG is a substrate for hexokinase, [^{14}C]-FDG was incubated with purified hexokinase and ATP in vitro, and the reaction products were analyzed for evidence of [^{14}C]-fluorodeoxyglucose phosphate formation. The reaction mixture consisted of 33 mM Tris-chloride, 7 mM $MgCl_2$, 7 mM ATP, 8.3 mM [^{14}C]-FDG (specific activity = 0.38 μCi/μmol), and 0.03 mg (4.2 U) of yeast hexokinase (Boehringer Manheim) at pH 7.8 in a final volume of 3.0 ml (Bessell and Thomas, 1973a). The incubation was carried out for 20 minutes at 37°C, and 0.5-ml samples were removed at zero time and after 10 and 20 minutes of incubation. The protein in the samples was precipitated with 6% perchloric acid and removed by centrifugation. The perchloric acid was neutralized with K_2CO_3, and the precipitated $KClO_4$ was also removed by centrifugation. The supernatant solution was then evaporated to dryness under vacuum, and the residue was redissolved in 10 μl of water and chromatographed on cellulose MN 300 (Analtech, Inc.) thin layer chromatographic plates in a solvent system consisting of isobutyric acid-ammonia-H_2O (66:1:33, vol/vol/vol) (Ido et al., 1978). The plates were then dried and scanned for radioactivity with a Packard radiochromatogram scanner (Packard Instrument Co.).

The suitability of [^{14}C]-FDG as a tracer for cerebral glucose consumption was further examined by using it exactly as though it were [^{14}C]-DG in a typical measurement of local cerebral glucose utilization by the [^{14}C]-DG autoradiographic technique (Sokoloff et al., 1977). The experiment was carried out in two normal, conscious, adult albino rats weighing approximately 300 g. Approximately 10 μCi of [^{14}C]-FDG were administered as an intravenous pulse at zero time, and timed arterial blood samples were drawn during the subsequent 30 minutes for assay of their plasma [^{14}C]-FDG and glucose concentrations. At 30 minutes the rat was decapitated, and the brain was removed, frozen, and sectioned and autoradiographed as previously described (Reivich et al., 1969). Local cerebral glucose utilization was calculated from the measured plasma and tissue ^{14}C concentrations as though the tracer used were [^{14}C]-DG.

Calculation of the Radiation Dosimetry in Man Based on the Organ Distribution of [^{18}F]-FDG in Dogs

To calculate the absorbed radiation dose, preliminary distribution studies were performed in rats in which the time course of distribution of [^{14}C]-DG was determined. Six rats were killed at 1, 2, and 4 hours after the intravenous injection of a bolus of [^{14}C]-DG, and the activity in various organs was assayed. This information allowed us to calculate the biological half-life of DG in various organs and to choose an optimum time to study the distribution of FDG in the body. On the basis of these results, two dogs were studied 1 hour after an intravenous bolus injection of [^{18}F]-FDG, and the distribution of ^{18}F activity in various organs was determined (Gallagher et al., 1977).

Radiation dosimetry calculations were based on

TABLE 1 *Biological Half-Life of DG in the Rat*

Organ	$t_{1/2}$ (hr)
Lung	1.8
Kidney	0.9
Heart	5.6
Liver	3.9
Spleen	25
Fat	21
Brain	7.2

the organ distribution at 60 minutes (Gallagher et al., 1977), and were calculated according to the MIRD* model, using the following assumptions: (1) after an intravenous injection of 1 mCi of [^{18}F]-FDG, kidneys, lungs, liver, brain, heart, spleen, ovaries, and bladder instantaneously and uniformly take up the amounts of activity determined by the tissue distribution at 60 minutes in dogs; (2) the remainder of the activity is instantaneously and uniformly distributed throughout the whole body; and (3) the effective clearance half-time is 1.83 hours ($t_{1/2}$ of ^{18}F) for all organs since, in most cases, it is rapid compared to the biological half-lives as determined in rats with [^{14}C]-DG (Table 1).

Toxicity Studies

Six BNL strain adult mice were injected intraperitoneally with FDG, 14.3 mg/kg (1000 × human dose), at weekly intervals for 3 weeks (total of 3000 × human dose), given food and water ad libitum, and observed over the 3-week period. A comparable group of six mice were injected intraperitoneally with the same volume of sterile saline on the same schedule, given food and water ad libitum, and observed for 3 weeks. The mice were weighed weekly, and after 3 weeks were killed and their internal organs examined grossly and microscopically.

Two adult female conditioned beagle dogs were injected intravenously with FDG, 0.72 mg/kg (50 × human dose), at weekly intervals for 3 weeks (total of 150 × human dose). Another adult female conditioned beagle received the same volume of sterile saline intravenously. Baseline, 2-hour, 1-week, and 2-week blood and urine samples were obtained for analysis. A few cerebrospinal fluid samples were also collected. The following analyses were performed: (1) *Urine:* physical and microscopic examination, electrolytes, creatinine, glucose, protein, urobilinogen, and osmolarity. (2) *Blood:* RBC, WBC, platelets, reticulocytes, differential, hemoglobin, hematocrit, sedimentation rate, pro-time, osmolarity, electrolytes, glucose, urea nitrogen, uric acid, creatinine, alkaline phosphatase, LDH, SGOT, SGPT, CPK, total protein, albumin, and total bilirubin. (3) *Cerebrospinal fluid:* glucose, protein, and chloride. At the end of 3 weeks the dogs were killed with an overdose of intravenous pentobarbital, and their internal organs were examined grossly and microscopically.

Determination of Local Cerebral Glucose Consumption in Man

Two normal male volunteers aged 26 and 24 were studied after their informed consent was obtained. Each subject's brachial artery was catheterized percutaneously and an intravenous infusion of physiologic saline was started. The subject was made comfortable in the Mark IV brain scanner, his head held firmly in position with respect to the detectors by a rigid foam head holder cast individually for each subject. After a period of at least 30 minutes was allowed for the subjects to attain a steady control state, a bolus of [^{18}F]-FDG (5.3 mCi in the first subject, 8.2 mCi in the second) was administered. The specific activities of the [^{18}F]-FDG were 8.9 and 8.8 mCi/mg, respectively, at the time of injection.

The [^{18}F]-FDG method for determination of local cerebral glucose metabolism requires knowledge of both the arterial blood plasma glucose and [^{18}F]-FDG concentrations as a function of time following an intravenous bolus injection of [^{18}F]-FDG. These concentrations must be monitored from the time of injection of the [^{18}F]-FDG until a time greater than 30 minutes later, when the brain tissue ^{18}F activity is quantitatively determined in three dimensions by means of a tomographic brain scan. Since the plasma glucose concentration is in a steady state during the time of the study (0–120 minutes), 2.0-ml blood samples were drawn from the arterial catheter only every 10–15 minutes for glucose determination. The blood samples were centrifuged and a protein-free filtrate made from the separated plasma by the Somogyi method (Somogyi, 1937). These samples were analyzed for glucose concentration by an enzymatic technique (Saifer and Gerstenfeld, 1958), using glucose oxidase (Glucostat, Worthington Biochemical Corp.) in barium-zinc filtrates (Nelson, 1944).

The time course of the arterial plasma ^{18}F activity following the bolus injection was determined by periodically drawing 2.5-ml samples, initially at 15-second intervals and then over progressively longer intervals, as seen in Figure 1. These samples were centrifuged, and the plasma was assayed for ^{18}F activity in a NaI(Tl) well counter (Packard model 3002). The activity was corrected for decay by adjusting all values back to the time of injection. Standard samples containing ^{68}Ga obtained from a cylinder used to calibrate the detectors on the Mark IV scanner were counted along with the plasma samples to provide a standard reference for efficiency correction between the Mark IV and the well counter (see below). The counts from these standards also were corrected for decay back to the time of injection.

*MIRD, Journal of Nuclear Medicine, Supplements 1–4 (1968, 1969, 1970).

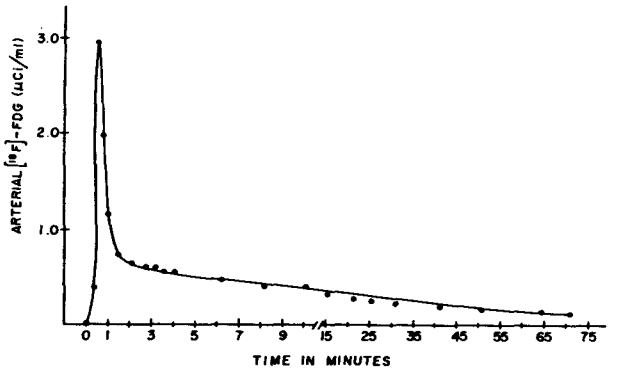

FIGURE 1 *Time course of arterial [^{18}F]-2-deoxy-2-fluoro-D-glucose ([^{18}F]-FDG) concentration in man following an intravenous bolus injection at time zero.*

Thirty minutes after the injection of [^{18}F]-FDG, the first scan was started. Each scan required 9–12 minutes to complete, depending on the count rate obtained. Three and seven scans, respectively, were obtained in the two subjects at +1, +2, and +4 cm in relation to the orbital-meatal line in the first subject and at −1, +1, +3, +4, +5, +6, and +7 cm in the second. Once the ^{18}F concentration was determined in the section matrix by reconstruction, as described above, the entire concentration distribution was corrected for decay back to the time of [^{18}F]-FDG injection. Immediately prior to the study, a section scan was made of a phantom cylinder containing a uniform concentration of ^{68}Ga in water. ^{68}Ga is a positron-emitting radionuclide from a commercially available ^{68}Ga generator, and is an ideal radionuclide for calibration for the positron emission of ^{18}F. The data from the cylinder scan and the counting of a sample of the ^{68}Ga solution from the cylinder in the NaI(Tl) well counter allow one to determine the ratio of the efficiency of the Mark IV scanner to that of the well counter used to count the ^{18}F activity in the plasma samples.

With the information concerning the arterial specific activity of [^{18}F]-FDG and the distribution of ^{18}F activity in the brain, it is possible to calculate the rate of local cerebral glucose consumption using Equation 1, where now $C_{\dagger}^{*}$ = the concentration of FDG-6-PO_4 in the tissue; C_p^* = the arterial plasma concentration of FDG; k_1^*, k_2^*, and k_3^* are the rate constants for the transport from plasma to the tissue precursor pool, for the transport back from tissue to plasma, and for the phosphorylation of FDG in the tissue, respectively; λ = the ratio of the distribution volume of FDG in the tissue to that of glucose; and K_m^* and V_{max}^* = the kinetic constants of hexokinase for FDG.

$C_{\dagger}^{*}$ is obtained for each region of interest from the section scan; the time course of C_p^* and C_p are measured directly; the values of k_1^*, k_2^*, k_3^*, and the lumped constant that were used are discussed below under Results. Thus we are able to calculate the rate of glucose consumption, R, for any region of the brain.

Results

Biochemical Properties of FDG

Incubation in vitro of [^{14}C]-FDG with ATP and purified hexokinase resulted in a time-dependent

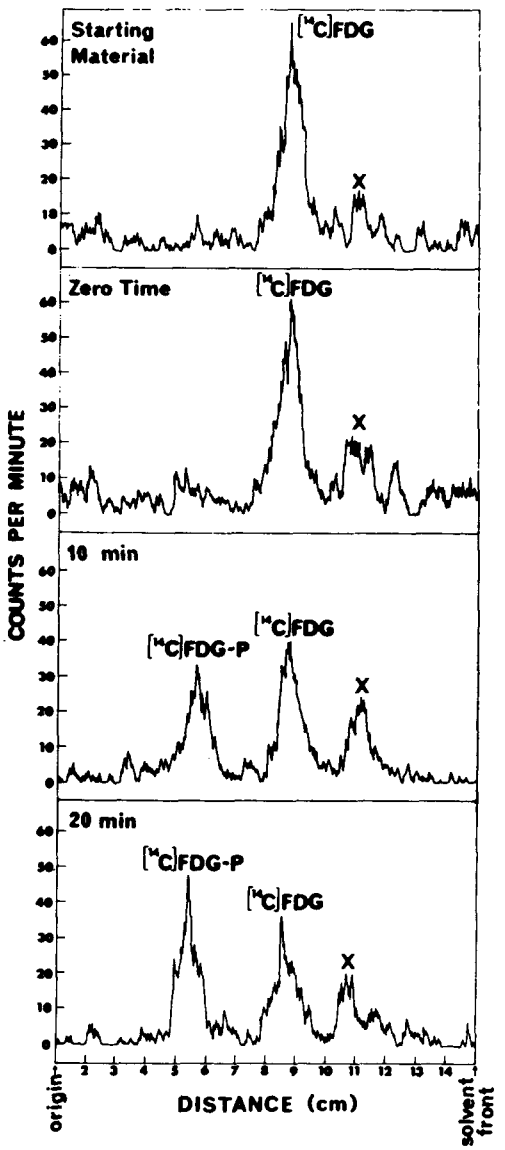

FIGURE 2 *Thin-layer chromatographic analysis of time-dependent transfer of radioactivity from [^{14}C]-FDG to a slower-moving compound with mobility like that of [^{14}C]fluorodeoxyglucose-6-phosphate during incubation in reaction mixture containing hexokinase and ATP. The composition of the reaction mixture and the chromatographic procedures are described in Methods. The times given in the figure represent the duration of incubation of the reaction mixture at 37°C. Incubation in absence of hexokinase or ATP resulted in no appearance of slower-moving peak.*

FIGURE 3 *Autoradiograms of brain sections from rats 30 minutes after an intravenous bolus injection of [^{14}C]-DG, [^{14}C]-FDG, or [^{14}C]-methylglucose. Note the similarity of the autoradiograms from the rats receiving [^{14}C]-DG and [^{14}C]-FDG and the lack of regional differentiation in the rat receiving [^{14}C]-methylglucose, indicating that local metabolism rather than blood flow and transport determines the local tissue concentration of ^{14}C at long intervals after a pulse of either [^{14}C]-DG or [^{14}C]-FDG.*

decrease in the chromatographic peak corresponding to [^{14}C]-FDG and its partial replacement by a slower-moving peak (Fig. 2). No standard of fluorodeoxyglucose phosphate was available with which to identify this slower peak positively as that of [^{14}C]-fluorodeoxyglucose phosphate. Its mobility, however, was slower than that of both DG and deoxyglucose-6-phosphate, and bore the same relationship to the mobility of [^{14}C]-FDG as the mobility of deoxyglucose-6-phosphate did to that of DG. Furthermore, its formation was fully dependent on the presence of ATP and hexokinase in the incubation mixture. The appearance of a labeled derivative of [^{14}C]-FDG that was dependent on time and on the presence of both hexokinase and ATP, and that corresponded to neither [^{14}C]-DG nor [^{14}C]-deoxyglucose-6-phosphate, was considered as presumptive evidence that FDG is converted to fluorodeoxyglucose phosphate by hexokinase. An unidentified radioactive contaminant present in the original batch of [^{14}C]-FDG used in these experiments, peak X in the chromatograms, was unaffected by the incubation procedure.

The autoradiographs obtained from sections of the brains of the two rats administered [^{14}C]-FDG were identical in character to those obtained with [^{14}C]-DG and entirely different from those seen with 3-O-methyl-[^{14}C]glucose, which is not phosphorylated by hexokinase (Fig. 3). Indeed, when local cerebral glucose utilization was calculated in this experiment with the same rate constants and lumped constant determined for [^{14}C]-DG, the values obtained for the local rates of glucose metabolism for various structures were distributed similarly ($r = 0.989$, $P < 0.001$) and were only moderately lower than those obtained with [^{14}C]-DG (Table 2). These results indicate that FDG is essentially as suitable a tracer for the technique as DG, but is probably associated with a lumped constant somewhat lower than that of [^{14}C]-DG.

The exact value for this constant will have to be determined in man, but for these studies a value

TABLE 2 *Local Cerebral Glucose Metabolism in the Rat*

Structure	[^{14}C]-DG (8 rats) (mg/100 g per min)	[^{14}C]-FDG (2 rats) (mg/100 g per min)
Gray matter		
Visual cortex	20.3	17.0
Auditory cortex	29.3	21.0
Lateral geniculate	16.9	14.0
Superior olive	26.5	21.5
Lateral lemniscus	20.5	17.9
Inferior colliculus	36.5	27.4
Superior colliculus	18.0	13.2
White matter		
Internal capsule	5.9	5.5
Cerebellar white matter	6.7	6.1

17.9% lower than that determined for DG in the monkey has been used, since on the average the values of regional glucose consumption obtained with FDG were 17.9 ± 2.5% (SE) lower than those obtained with DG (Table 2). The value of the lumped constant for DG in the awake monkey is 0.344 ± 0.036 (SE) (Sokoloff, unpublished observations). Therefore, a value of 0.282 was used in the present study.

The values of k_1^*, k_2^*, and k_3^* for FDG will also have to be determined. However, since Equation 1 is relatively insensitive to changes in these values, and since there was only a 17.9% difference in the calculated values of regional glucose consumption in toto, the values for these constants previously determined for DG in rats (Sokoloff et al., 1977) were used (Table 3).

Organ Distribution of DG and Radiation Dose

The radiation doses to selected organs were calculated as described under Methods from previously reported tissue distribution data for dogs

TABLE 3 *Values of Rate Constants for DG in the Normal Awake Rat*

	Rate constants (min^{-1})		
	k_1*	k_2*	k_3*
Gray matter	0.189 ± 0.012	0.245 ± 0.040	0.052 ± 0.010
White matter	0.079 ± 0.008	0.133 ± 0.046	0.020 ± 0.020

Results are expressed as mean ± SE.
From Sokoloff et al. (1977).

TABLE 4 *Radiation Dosimetry for ^{18}FDG in Man*

Organ	Dose (mrad/mCi)
Whole body	43
Ovaries	63
Liver	67
Kidneys	77
Lungs	67
Brain	66
Heart	147
Spleen	185
Bladder	289

(Gallagher et al., 1977). The calculated absorbed radiation doses to these organs in man are shown in Table 4.

Toxicity Studies

Mice injected with FDG (14.3 mg/kg × 3) suffered no immediate or long-term effects. Their weight remained stable and did not differ significantly from that of the controls (see Table 5). No gross or microscopic abnormalities were present in the brain, heart, spleen, liver, kidneys, or lungs.

The dogs injected with FDG (0.72 mg/kg × 3) showed no clinical signs or symptoms of adverse effects. No significant abnormalities were detected in the blood, urine, or cerebrospinal fluid analyses, and no significant gross or microscopic abnormalities were present in the brain, heart, spleen, liver, kidneys, lungs, ovaries, or intestines.

The injected dose in man is approximately 1 mg of [^{18}F]-FDG (0.014 mg/kg), a factor of 150 times less than the total dose administered without effect to dogs, a factor of 3000 times less than the total dose administered without effect to mice, and a factor of 43,000 times below the LD_{50} for rats previously reported (Bessell et al., 1973).

Local Cerebral Glucose Consumption in Man

The arterial [^{18}F]-FDG concentration curve from one of the subjects is shown in Figure 1. This curve has been corrected for isotope decay back to the time of injection of the bolus of [^{18}F]-FDG.

Representative section scans from one subject are shown in Figure 4. The level at which these scans were performed is indicated in relation to the orbito-meatal line on a rectilinear scan of the subject's head.

In Figure 5 the individual scans are shown along with an illustration of a slice through the human brain at approximately the same level. Indicated are representative values for the calculated regional rate of glucose utilization in mg/min per 100g of brain.

In Table 6 are the calculated values of local glucose consumption for various cerebral structures in the two subjects.

Discussion

FDG was chosen as a tracer for this method because it could be labeled with a positron emitter (^{18}F) which could be detected externally, and because previous studies had demonstrated that DG was a suitable tracer for glucose metabolism in the brain (Sokoloff et al., 1977). DG differs from glucose in that a hydrogen atom replaces the hydroxyl group at the second carbon atom of the molecule. DG has been shown to enter tissues and cells rapidly (Wick et al., 1955), to be phosphorylated by brain hexokinase to DG-6-PO_4 (Sols and Crane, 1954), and not to be further metabolized (Sols and Crane, 1954; Tower, 1958; Bachelard, 1971; Horton et al., 1973). DG-6-PO_4 is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase (Sols and Crane, 1954). It is transported from the blood into the brain by the same saturable carrier mechanism that transports glucose (Bachelard, 1971; Horton et al., 1973; Bidder, 1968). Once it is phosphorylated to DG-6-PO_4 it remains in the tissue in that form. It is essentially "trapped" in the location at which it is phosphorylated, since the half-life of DG-6-PO_4 is approximately 8 hours in gray matter and 10 hours in white matter (Sokoloff et al., 1977). The activity of glucose-6-phosphatase, an enzyme that might be expected to hydrolyze deoxyglucose-6-phosphate, is reported to be very low in mammalian brain (Hers and DeDuve, 1950; Raggi et al., 1960; Prasannan and Subrahmanyan, 1968). It has been shown that deoxyglucose-6-phosphatase activity in the brain is negligible in relation to this technique (Sokoloff et al., 1977). These characteristics made DG a suitable candidate for the development of an autoradiographic technique for

TABLE 5 *Mice: Weight (g)*

	Agent	Baseline	1 Week	2 Weeks	3 Weeks
Control	Saline	28.57 ± 2.74	29.98 ± 3.17	31.35 ± 2.18	32.90 ± 2.99
Experimental	FDG	29.43 ± 1.07	30.32 ± 1.23	30.80 ± 0.98	30.85 ± 1.05

Results are expressed as mean ± SE.
From Som, P., and Atkins, H. IND application #13483 (unpublished observations).

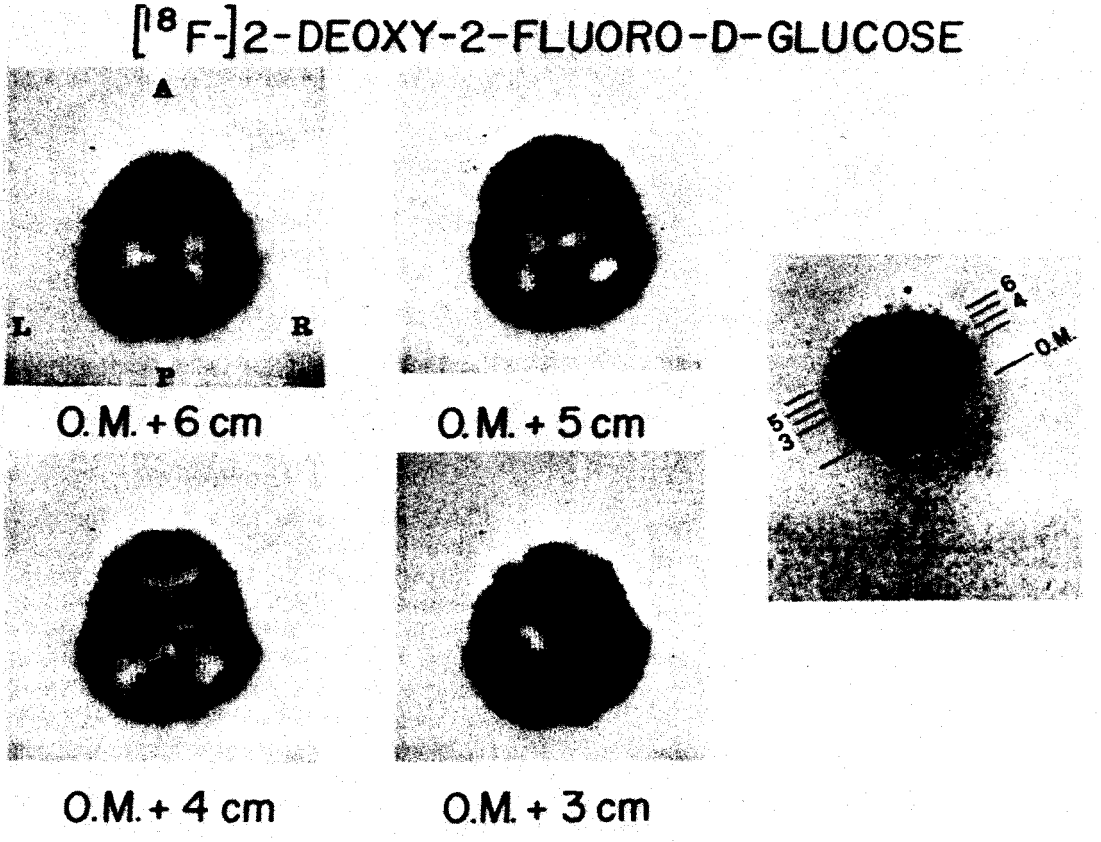

FIGURE 4 *Section scans of the head beginning 30 minutes after an intravenous bolus injection of [^{18}F]-FDG. The level of each scan is indicated in relation to the orbito-meatal (O.M.) line on a rectilinear scan of the subject's head. A = anterior, P = posterior, L = left, and R = right.*

the measurement of local cerebral glucose metabolism in animals. It should be noted that DG in sufficiently high concentrations inhibits the transport and utilization of glucose (Tower, 1958), partly because of a depletion of available ATP for the hexose-catalyzed phosphorylation of glucose, but mainly by competitive inhibition of phosphohexokinase isomerase by deoxyglucose-6-phosphate. Therefore, DG must be used in trace amounts so as to have no effect on glucose metabolism. DG has been successfully used in animals to measure local cerebral glucose utilization in various states of anesthesia (Shapiro et al., 1975), in awake animals (Sokoloff et al., 1977), during induced seizures (Kennedy et al., 1975), and following middle cerebral artery occlusion in the cat (Ginsberg et al., 1977).

The substitution of a fluorine atom for a hydrogen atom on the second carbon (C-2) of the DG molecule does not alter its metabolic fate significantly. It has been demonstrated previously that FDG is phosphorylated by hexokinase to 2-deoxy-2-fluoro-D-glucose phosphate (Bessell et al., 1972), and that this compound is a relatively poor substrate for glucose-6-phosphate dehydrogenase (Bessell and Thomas, 1973b). It should be noted that modification of the glucose molecule at C-2 (i.e., 2-DG and 2-FDG) does interfere with its ability to undergo active transport (Barnett and Munday, 1972), but since brain glucose transport is a carrier-mediated process, it is not necessary that the substrate possess the structure required for active transport. It has been shown (Bachelard, 1971) that glucose and DG share the same transport systems facilitating entry across the blood-brain barrier, thus demonstrating that this structural modification at C-2 does not interfere with carrier-mediated transport, although it does interfere with active transport.

Although there is some evidence suggesting that FDG is a nonreversible inhibitor of glucose phosphorylation (Coe, 1972), this is not likely to cause a significant effect on glucose metabolism in the present method, in which FDG is used in tracer amounts. It is estimated that the peak concentration of FDG in the brain is 0.3 μM, which is approximately 1/3000th of the concentration found to produce 33% inhibition in vitro (Coe, 1972). At this concentration, the amount of inhibition present would be expected to be negligible.

A direct comparison of the use of these two tracers (DG and FDG) for the determination of local cerebral glucose consumption by the autora-

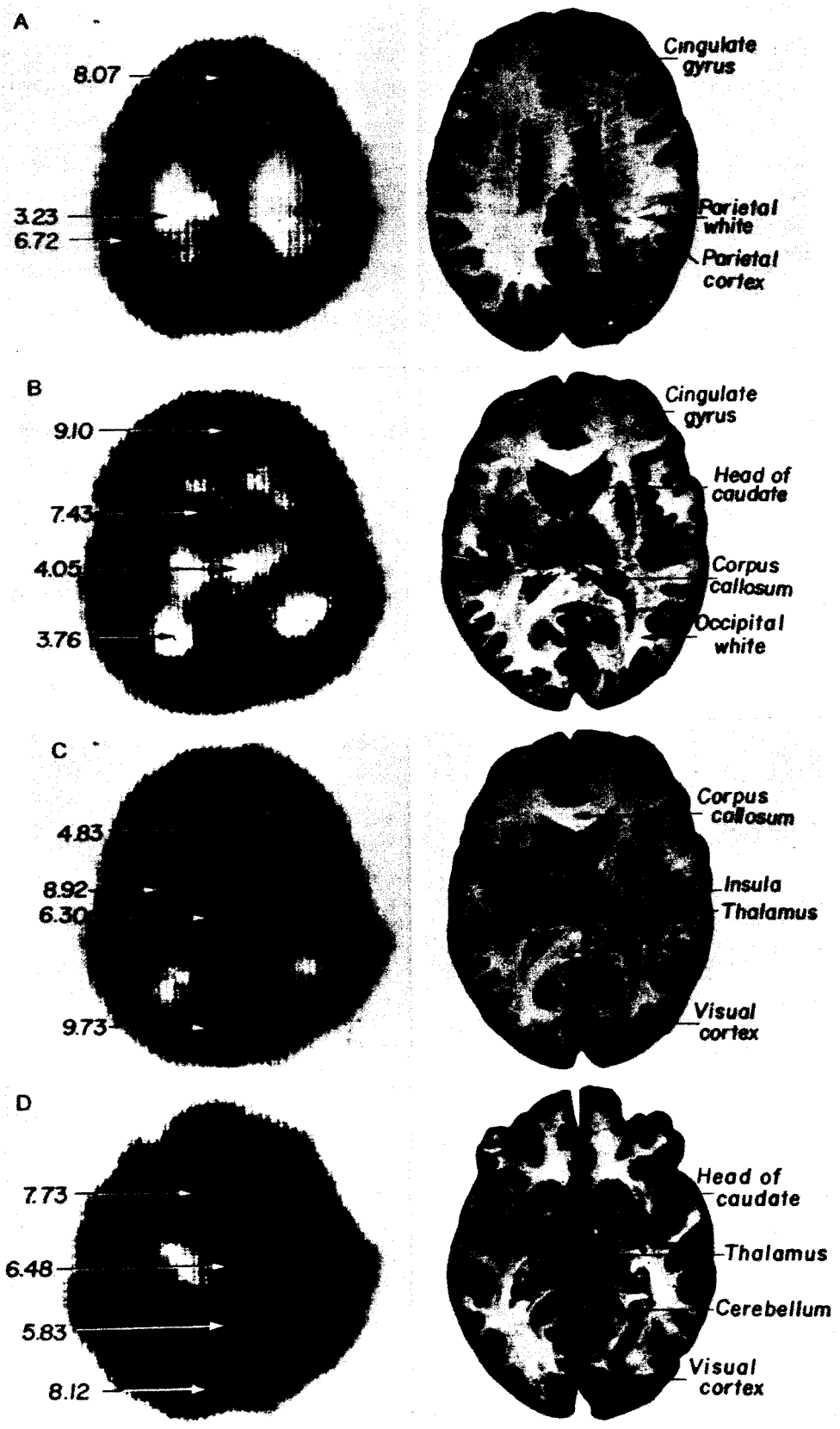

FIGURE 5 *Section scans of the head and photograph of a slice through the human brain at approximately the same level. The numbers represent the local cerebral metabolic rate for glucose in mg/100 g per minute in the structure labeled: (A) scan at O.M. + 6 cm level; (B) scan at O.M. + 5 cm level; (C) scan at O.M. + 4 cm level; and (D) scan at O.M. + 3 cm level.*

TABLE 6 *Local Cerebral Glucose Metabolism in Man*

	$LCMR_{gl}$ (mg/100 g per min)	
	Subject 1	Subject 2
Gray matter		
Visual cortex	11.24	9.30
Thalamus	8.79	6.06
Frontal cortex	8.15	8.43
Sensory-motor cortex	8.17	8.75
Parietal cortex	6.02	7.65
Temporal cortex		8.12
Hippocampus		5.85
Caudate nucleus	6.47	7.23
Putamen	6.09	6.74
Amygdala		6.23
Cerebellum		5.79
White matter		
Frontal white matter	2.37	4.91
Parietal white matter	3.88	3.54
Occipital white matter	4.69	3.76
Corpus callosum	3.22	4.05

diographic technique in the rat gave comparable results. The correlation between the two sets of data for 10 different structures in the brain was excellent ($r = 0.989$). There was a small but systematic difference between the values obtained with the two tracers, those obtained with FDG being lower. This is probably due to a slightly lower value for the lumped constant for FDG compared to DG. The exact value for this constant will have to be determined for man, but for the present a value 17.9% lower than that determined for DG in the awake monkey has been used.

With this value of the lumped constant and the values of the kinetic constants in Table 3, we were able to calculate values for local cerebral glucose utilization for various structures in the brain of normal man.

It should be noted that the value of the lumped constant may be altered in diseased brain tissue, and it must therefore be evaluated before local cerebral metabolic rates can be quantified in such conditions. The operational equation is relatively insensitive to changes in the kinetic constants for FDG (i.e., k_1^*, k_2^*, and k_3^*), which influence the rate of clearance of unmetabolized FDG, and therefore the effect of disease states on these parameters will probably only negligibly affect the calculated values for local cerebral metabolic rate. However, this supposition will have to be demonstrated before the method is used under such conditions.

TABLE 7 *Values of Average Brain Metabolic Rate for Glucose in Man from Literature*

	CMR_{gl} (mg/100 g brain tissue per min)
Scheinberg and Stead, 1949	6.04 ± 0.24
Novack et al., 1953	6.5 ± 1.2
Gottstein et al., 1963	5.30 ± 0.96
Cohen et al., 1967	4.48 ± 0.29
Takeshita et al., 1972	5.57 ± 0.79
Present study	5.9

Results are expressed as mean ± SE.

TABLE 8 *Comparison of Local Cerebral Glucose Metabolism in Primates*

	$LCMR_{gl}$ (mg/100 g per min)	
	Man	Monkey*
Visual cortex	10.27	8.73
Thalamus	7.42	7.10
Frontal cortex	8.29	7.76
Sensory-motor cortex	8.46	8.09
Parietal cortex	6.84	8.42
Temporal cortex	8.12	8.26
Hippocampus	5.85	6.16
Caudate nucleus	6.85	8.66
Putamen	6.42	10.56
Amygdala	6.23	6.91
Cerebellum	5.79	8.61
Subcortical white matter	3.80	2.12

* From Reivich et al. (unpublished observations).

There are no local cerebral glucose data available for man with which to compare the present results. However, an average value for cerebral glucose consumption can be calculated from our data and compared with such values in the literature. The value calculated was a weighted average based on the approximate volume of each structure measured. This gave an average gray matter value of 8.05 mg/100g per minute, an average white matter value of 3.80 mg/100g per minute, and an average whole brain value of 5.9 mg/100g per minute. The last figure compares favorably with values in the literature (Table 7). Regional values of cerebral glucose consumption are available in other awake primates with which these data can be compared (Table 8). There is good agreement between the values for various regions of the brain ($r = 0.581$; $n = 12$; $P < 0.05$).

On the basis of these studies, we feel that FDG is a suitable tracer for the measurement of local cerebral glucose metabolism, and that the same model that was used for DG can be applied to FDG. This has enabled us to measure quantitatively local cerebral glucose metabolism in man for the first time (Reivich et al., 1977). The method has since been applied to make qualitative measurements in patients with cerebrovascular disease (Kuhl et al., 1977b).

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